

Neurogenic Inflammation: With Additional Discussion of Central and Perceptual Integration of Nonneurogenic Inflammation

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The Working Group on Neurogenic Inflammation proposed 11 testable hypotheses in the three domains of neurogenic inflammation, perceptual and central integration, and nonneurogenic inflammation. The working group selected the term people reporting chemical sensitivity (PRCS) to identify the primary subject group. In the domain of neurogenic inflammation, testable hypotheses included: PRCS have an increased density of c-fiber neurons in symptomatic tissues; PRCS produce greater quantities of neuropeptides and prostanoids than nonsensitive subjects in response to exposure to low-level capsaicin or irritant chemicals; PRCS have an increased and prolonged response to exogenously administered c-fiber activators such as capsaicin; PRCS demonstrate augmentation of central autonomic reflexes following exposure to agents that produce c-fiber stimulation; PRCS have decreased quantities of neutral endopeptidase in their mucosa; exogenous neuropeptide challenge reproduces symptoms of PRCS. In the domain of perceptual and central integration, testable hypotheses included: PRCS have alterations in adaptation, habituation, cortical representation, perception, cognition, and hedonics compared to controls; the qualitative and quantitative interactions between trigeminal and olfactory systems are altered in PRCS; higher integration of sensory inputs is altered in PRCS. In the domain of nonneurogenic inflammation, testable hypotheses included: increased inflammation is present in PRCS in symptomatic tissues and is associated with a heightened neurosensory response; PRCS show an augmented inflammatory response to chemical exposure. The working group recommended that studies be initiated in these areas. — *Environ Health Perspect* 105(Suppl 2):531–537 (1997)

Key words: neurogenic inflammation, perceptual and central integration, inflammation, chemical sensitivity

Introduction

The goal of the Working Group on Neurogenic Inflammation was to formulate specific testable hypotheses to explain the relationship between exposure and

symptoms in people reporting chemical sensitivities. The working group designated people reporting chemical sensitivity (PRCS) as the phrase to identify the group

of primary interest. For specific research projects, the working group emphasized the importance of certain hypotheses, clearly stated subject selection criteria, uniform subject characterization methods, and inclusion of appropriate controls.

The group identified three broad domains in which hypotheses could be generated: neurogenic inflammation, perceptual and central integration, and inflammation. Neurogenic inflammation was the initial assigned task of the group. However, some group members thought perceptual and central integration or nonneurogenic inflammation likely were the domain of primary dysfunction. Figure 1 indicates the likely interactions between these three domains.

The working group focused on understanding symptoms and processes that occur minutes, hours, or days after low-level chemical exposure. The group limited experimental questions to those that could be performed using existing methods and techniques. In the future techniques such as functional imaging may be useful but are insufficiently developed at present. Reagents for immunohistochemistry and immunoassays, and pharmacologic agents for human use are also developing rapidly.

The group thought individual research groups should specify their own definitions of chemical sensitivity but draw from previously proposed definitions. Subjects with diagnosed diseases may be included in research if controls include diseased subjects with and without chemical sensitivity. Studies may include subject groups with rhinitis and asthma, for which measures of short-term responses are well developed. Subjects with known psychiatric disease may also be included.

This paper presents definitions and general considerations for experimental

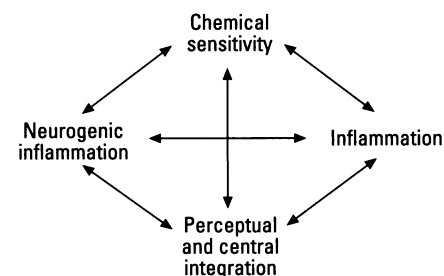


Figure 1. Potential interactions between chemical sensitivity and the domains of neurogenic inflammation, perceptual and central integration, and nonneurogenic inflammation.

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Abbreviations used: Ach, acetylcholine; CGRP, calcitonin gene related peptide; CO₂, carbon dioxide; MCS, multiple chemical sensitivity; NKA, neurokinin A; Nor, norepinephrine; NPY, neuropeptide Y; PRCS, people reporting chemical sensitivity; sub P, substance P; VIP, vasoactive intestinal peptide.

design and methods, followed by considerations specific to the domains of neurogenic inflammation, perceptual and central integration, and inflammation. Also included are the rationale for potential involvement of the domain, specific hypotheses, and selected references.

Definitions

People reporting chemical sensitivity:

The primary research subject group. The term multiple chemical sensitivity (MCS) or MCS-syndrome can be used as a research term provided there is an explicit research definition. The phrase chemical sensitivity may reflect several alterations in exposure-response relationships. Figure 2 illustrates terminology. The terms have been chosen because committee members thought they had common usage across disciplines of physiology and psychology.

Irritation: An excessive response to stimulation, i.e., specifically a condition of soreness or inflammation. Many chemicals stimulate c-fiber nerves; patients report having excessive responses. At present, it is unknown whether the response is characterized by soreness (acute discomfort) or induction of inflammation.

Increased response: An inclusive term that can mean increased sensitivity, increased reactivity, and prolonged duration.

Increased sensitivity: A leftward shift in the exposure-response curve.

Increased reactivity: An increase in the slope or the maximum of the exposure-response curve.

Increased duration: An increase in the duration of the response.

Threshold for symptoms: The point on the exposure-response curve at which symptoms are reported by the subject.

Habituation: Over time, the repeated presentation of a stimulus elicits a response of diminished amplitude.

Adaptation: The tendency, characteristic of a sensory organ, to show a diminished response as a result of prolonged or short-term repetitive stimulation.

Peripheral neural pathways: Peripheral nerves innervating organs contain both afferent and efferent neural pathways. Chemosensitive c-fiber nerves are afferent nerves that may have efferent functions through the axon reflex (Figure 3). Neuropeptides contained in c-fiber nerves include substance P (sub P), calcitonin gene-related peptide (CGRP), and neurokinin A (NKA). Efferent nerves include the sympathetic nerves and parasympathetic nerves. Sympathetic neurotransmitters include

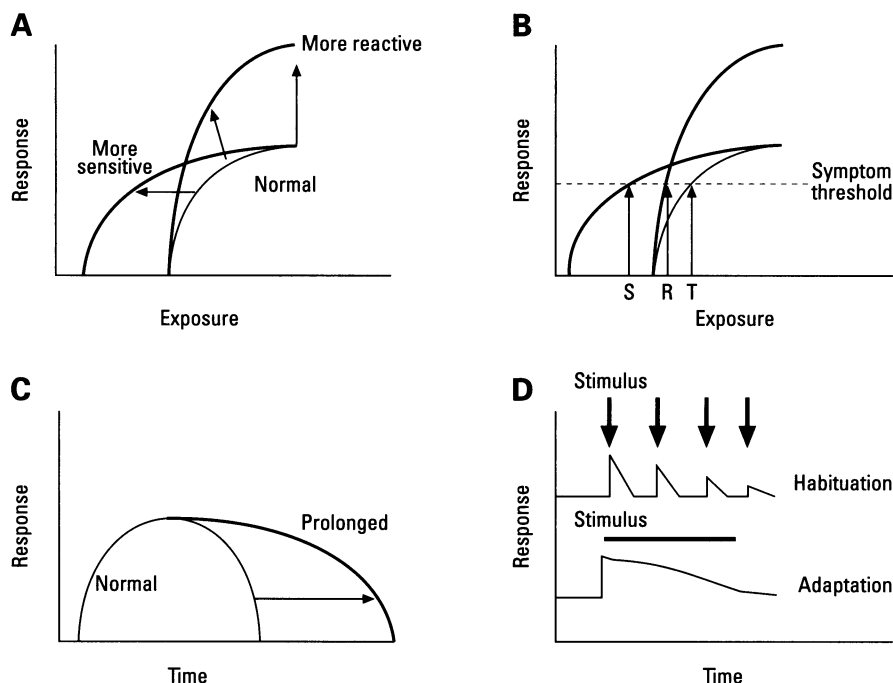


Figure 2. Illustration of terminology. (A) More sensitive denotes a decrease in the magnitude of exposure required to initiate the response; more reactive denotes an increase in the slope or in the maximum level of the exposure-response curve. (B) The threshold for perceiving symptoms may occur in the mid-position of the exposure-response curve (T). As a result, the clinical report of increased sensitivity could mean that the individual has become more reactive (R) or more sensitive (S). (C) Recognition of symptoms may require that the response be present for a certain duration. The clinical report of increased sensitivity could mean that the response has become more prolonged. (D) Habituation is the decrease in the amplitude of the response that occurs with repeated presentation of a stimulus. Adaptation is a progressive decrease in the magnitude of the response with prolonged presentation of a stimulus. The term adaptation is sometimes used to describe both adaptation and habituation, as defined above.

norepinephrine (Nor) and neuropeptide Y (NPY). Parasympathetic nerves contain acetylcholine and vasoactive intestinal peptide (VIP). The importance of each neural pathway in overall organ function or specific cell function depends on the density of nerve fibers, proximity to target sites, and the presence of specific receptors on target tissues.

Trigeminal nerve: The trigeminal nerve innervates the face and divides into the ophthalmic, maxillary, and mandibular branches (1). The trigeminal nerve innervates the respiratory mucosa that first contact inhaled irritants. The trigeminal nerve contains afferent and efferent nerves. Upper respiratory tissue is densely innervated with c-fiber nerves in the epithelium, glands, and vessels (1). Neuropeptide receptors are widespread in mucosal tissues. Efferent cholinergic fibers typically stimulate glandular secretion, whereas adrenergic fibers alter vascular tone.

Neurogenic inflammation: Neurogenic inflammation is initiated by stimulation of peripheral c-fiber neurons (2-4) (Figure 3). A peripheral axon reflex results in the release

of neuropeptides and in signs of inflammation at a peripheral sites distinct from the site of the original stimulus. The stimulus is also transmitted centrally and provides a central afferent signal and efferent reflexes.

Perceptual and central integration: Perceptual and central integration describes the process by which peripheral stimuli are delivered, processed, and interpreted by the central nervous system. Anatomic elements of central representation include primary and secondary projection and association areas. Functional elements of perceptual and central integration include quality coding, intensity, cognitive (discrimination), hedonic evaluation, and integration of information from other sensory receptors.

Inflammation: Inflammation is a dynamic process that may be initiated by diverse stimuli (e.g., allergen, infection, injury) and is characterized by diverse features (e.g., degree of edema, dominant cell type, degree of structural tissue alteration), and diverse sequelae (complete resolution, chronic inflammation, resolution with scarring). Typical features of inflammation

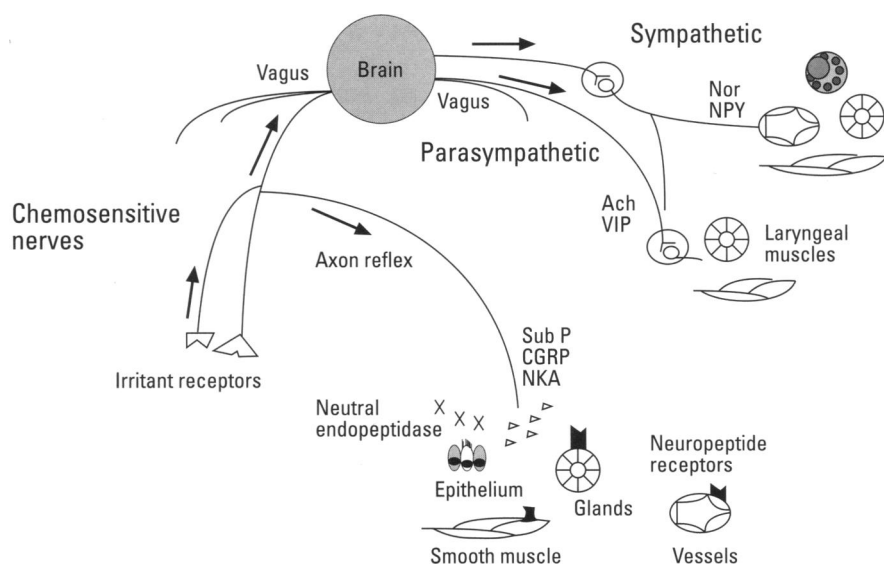


Figure 3. Anatomic elements of the response to chemosensitive nerve stimulation. Stimulation of the c-fiber nerves results in a peripheral axon reflex with release of neuropeptides sub P, CGRP, and NKA. The neuropeptides may be inactivated by neutral endopeptidase, an enzyme present in the mucosa, or may bind to receptors present on the epithelium, glands, smooth muscle, or vessels. Stimulation of the nerves may also result in a central afferent stimulus, with activation of parasympathetic nerves and sympathetic nerves. The neurotransmitters for these nerves are Ach and VIP (parasympathetic) and Nor and NPY (sympathetic).

are rubor (erythema, vasodilatation), calor (heat), turgor (edema), dolor (pain), and loss of function.

Experimental Design and Methods

Subject Selection

People reporting chemical sensitivity have signs or symptoms associated with exposures to a group of commonly encountered chemical inhalants such as products of combustion, cleaning products, pesticides, perfumes, and fragrances at levels encountered in daily life. The symptoms occur in one or more organ systems and often in many organs. Several research definitions encompassing these features have been published (5–7). Although no single case definition was endorsed by the work group participants, there was agreement that different selection criteria would be necessary for different studies, that chemically sensitive patients are a heterogeneous group, and subgroups might be selected in particular experiments. For example, subjects could be recruited on the basis of their dominant symptoms (neurocognitive, respiratory). A distinct onset of sensitivity with an identifiable exposure is not necessary for inclusion (as proposed by Cullen), and patients with insidious as well as acute onset of sensitivity symptoms may be studied.

Subjects with diagnosed diseases may be included in research if control groups include diseased subjects with and without chemical sensitivity (Table 1). Standard diagnostic criteria or research definitions for many diseases are published. Studies may include subject groups with rhinitis and asthma, for which measures of short-term responses are well developed and in association with which chemical sensitivity is commonly reported.

Subject Characterization

Characterization may include the duration and pattern of onset of symptoms (e.g., insidious vs abrupt), the subject's perception of the cause of symptoms [e.g., specific stressor(s)], current functional status, employment status, and current medico-legal issues (if any). The use of published questionnaires will assist in comparisons between studies.

Ethical Considerations and Protection of Human Subjects

Confidentiality

National Institute for Drug Abuse issues certificates of confidentiality for research that accumulates information of a potentially sensitive nature about a subject. The information derived in the study is then

not discoverable in medico-legal proceedings. Because of the complex medico-legal context of chemical sensitivity problems, investigators are encouraged to consult with this agency and to consider requesting a certificate of confidentiality.

Protection of Subjects

All protocols should be reviewed and approved by the local Institutional Review Board and written consent obtained for controlled exposures. Subjects typically are monitored by laboratory scientists and remain within voice reach during exposure sessions. Subjects are instructed in how to ask for help or to remove themselves from exposure and assured that they may promptly remove themselves from exposure at any time.

Exposure Conditions

Human exposure facilities allow careful control of the circumstances of exposure. The principle of using exposures equivalent to ambient exposures should be followed in establishing exposure regimens for people reporting chemical sensitivity. Attention should be given to the specificity of the stimulus. For example, studies have established that some agents act as selective trigeminal or olfactory stimuli. Blinding or masking may or may not be possible; interpretation of study results should consider the potential for bias in unmasked challenges (8).

Another use of controlled human exposure facilities is to examine the effect of removing agent exposures (e.g., filtering the air, removing point sources, providing special diets). As with exposure studies, interpretation of study results should consider the potential for bias in unmasked challenges.

Monitoring Risk

Pilot studies are appropriate with subsequent review to determine whether the risks are as predicted for people with chemical sensitivity. The principal investigator should closely monitor the responses of study subjects to determine whether typical symptoms are being elicited or whether a previously unknown adverse response is occurring.

Choice of Chemical for Challenges

The choice of chemical for the challenge exposures should take into consideration the portion of the respiratory tract where deposition of the chemical and interaction with the respiratory tract occur. For example, it is well known that water-soluble volatiles deposit almost exclusively in the

nasal passages (9). Formaldehyde is perhaps one of the best examples of a chemical that because of its reactive, water-soluble properties is deposited primarily in the nasal cavity and interacts with components of the nasal mucosa (10,11). Thus, on inhalation challenge the effects of formaldehyde should be directly related to initial interactions within this respiratory tract region. Water-soluble alcohols and ethers will also be deposited in the nasal passages; these chemicals can interact with specific receptors in the nasal mucosa, thereby initiating potential toxic effects or adverse responses. In contrast, water-insoluble volatiles are not entrained by the nasal mucosa and would therefore continue down the airways to be deposited in more distal regions (9).

Ozone is an example of a reactive chemical that will be deposited throughout the respiratory tract (12). However, because of regional anatomical and histologic differences, it reacts with respiratory mucosa primarily in the region of the nasal transitional epithelium and the respiratory bronchioles. Thus, effects on challenge with ozone should be either of an anterior nasal or a lower respiratory tract nature (13,14).

Finally, nonreactive water-insoluble organics will continue to the most distal portions of the respiratory tract and be absorbed into the blood because of the high perfusion of the alveoli. These types of chemicals, xylene, toluene, and hexane, for example, will be translocated in the blood to various targets in the central nervous system, including the brain. Complex mixtures such as cigarette smoke, gasoline exhaust, and diesel combustion products contain examples of each of the chemical classes listed above (15). Thus, these complex mixtures would be expected to exhibit upper and lower respiratory effects as well as distal central nervous system effects. The advantage of these complex mixtures is that they reproduce environmental stimuli that patients identify as triggers of symptoms.

Removal from exposure is also an intervention that may aid in understanding the disease process. An example of a question that could be posed using a unit is: Does residence in an environmental unit reduce indices of inflammation in patients with diseases known to be characterized by chronic inflammation?

Experimental Reagents and Methods

Experimental reagents and methods define the practical boundaries of experimentation and hypothesis testing. The committee

Table 1. Approach to selection of subjects and controls: disease, structure, and function.

	Subject reports chemical sensitivity, PRCS +	Subject does not report chemical sensitivity, PRCS –
Disease		
Diagnosable disease present, Dis +		
Diagnosable disease absent, Dis –		
Structure		
Histologic feature present, Path +		
Histologic feature absent, Path –		
Function		
Specific function or response present, Response +		
Specific function or response absent, Response –		

Table 2. Established outcome measures.

	Structural/mediator	Functional
Physical examination	Patency, erythema, edema, heat	Range of motion
End organ structure or function	Acoustic rhinometry (29) Computerized tomography Magnetic resonance imaging	Rhinomanometry Pulmonary function test Mucociliary clearance (30) Smell identification test (31) Neurocognitive batteries
Presence of edema	Histology: endothelial gaps Albumin (32,33) Kinins	Increased resistance to flow, tissue turgor
Reduced/abnormal airway surface fluid	Pathology of fast-frozen specimens, disc weight (34)	Tear film breakup (35)
Vasodilatation	Quantification of vascular area, redness, temperature	Congestion reversed with vasoconstrictors (36)
Inflammatory cell influx	Acute inflammatory cell influx (37) Chronic inflammatory cell influx	
Proinflammatory mediators	Cytokines Neuropeptides	
Structural changes	Basement membrane thickening Altered nerve density, tissue neuropeptide content (38–41), or neuropeptide receptors	
Epithelial integrity	Tracer uptake (42)	Mucosal transepithelial potential difference (43)
Functional responsiveness		Reactivity to challenge (29,33,34) Negative mucosal potential (20)
Central processing		Trigeminal evoked potentials (19) Olfactory evoked potentials (21)

primarily considered outcome measures that have previously been used in studies involving human subjects. Table 2 lists such measures, but the working group emphasized that each outcome measure should be proposed for use only in the context of a defined hypothesis, adequate rationale, and experimental design. Additionally, the need for new, objective outcome measures was recognized.

Domain 1: Neurogenic Inflammation

Neurogenic inflammation is a subset of inflammation but is given special attention in this paper, since it is initiated by

stimulation of chemosensitive c-fiber nerves. People reporting chemical sensitivity typically report that their symptoms are triggered by exposure to diverse chemicals. The structural diversity of agents initiating symptoms makes an allergic etiology unlikely, but structurally diverse chemicals do stimulate the irritant receptor (16). When agents stimulate c-fiber nerves, they may initiate an axon reflex, central processes (Figure 3), and sympathetic and parasympathetic reflexes.

The broad hypothesis is that the chemosensitive nerves, their products, and their receptors, are the critical end organs

in chemical sensitivity syndromes (17). Alterations in neurogenic inflammation could occur at the afferent irritant receptor in the control of the axon reflex (such as the density of nerve fibers, their neuropeptide content, the quantity of neuropeptide released with stimulation, and the area of release resulting from stimulation). Alterations could also occur at the level of the tissue neuropeptide receptor or intracellular transduction of the receptor stimulus (Figure 3). Alterations could also occur in central processing of the irritant stimulus (see "Domain 2: Perceptual and Central Integration") and in the control or expression of autonomic reflexes. Cell- and plasma-derived mediators generated during infectious or allergic inflammation may modulate neurogenic inflammation.

There are two versions of the neurogenic inflammation hypothesis. One hypothesis states that the inciting event or process is unknown. Once the process begins, the c-fiber nerves play a central role in the increased sensitivity and decreased specificity of responses as well as relay to and amplification of central reflexes. The adverse reaction to an exposure reflects the severity of the process, but the low-level chemical exposure does not materially alter the pathologic process. A separate hypothesis states that the initiating process for chemical sensitivity is chemically induced injury to the c-fiber neuron structure and function, and that the course and severity of the syndrome are a function of the magnitude of continuing exposure to the chemical, with injury progressing with low-level, symptom-inducing exposures.

Airborne chemicals can activate the sensory irritant receptor through two different mechanisms (16). First, the receptor can be activated by physical adsorption, which is believed to be the case for alkanes, alkylbenzenes, alcohols, ketones, and ethers. The alkylbenzenes activate the receptors via a benzene binding site and the alcohols activate the receptor via a hydrogen bond. Capsaicin, the active ingredient in red pepper, binds to the vanilloid receptor. Second, the other group of substances activates the receptor by a chemical reaction (16). In general, this group of substances is more potent than substances only physically adsorbed to the receptor. The chemically reactive substances can break a disulfide bond in the receptor, which is believed to be the mechanism by which sulfur dioxide activates the receptor. Many substances activate the receptor by a chemical reaction with a nucleophilic group.

Formaldehyde, acrolein and related substances, and chlorobenzylidene malononitriles and related substances all are expected to react with a thiol group in the receptor. Oxidizing agents such as chlorine and ozone may oxidize the thiol group and thereby activate the receptor. The thiol group might also be involved in the acid-based reactions responsible for the receptor activation process of amines. Other nucleophilic groups (HO^- or NH_2 groups) may be involved in the binding of isocyanates and some of the aldehydes.

c-Fiber nerves contain and release biologically active neuropeptides. Neuropeptides have been shown to influence the function of immune effector cells and epithelial structures such as epithelium, glands, and vessels. The presence and activity of neuropeptide receptors at tissue sites are important in determining the consequences of neuropeptide release (1). Enzymes that degrade neuropeptides, for example, neutral endopeptidase, are present in airway epithelium and may be oxidatively inactivated by tobacco smoke exposure (18). In addition to the peripheral axon reflex, concomitant generation of an afferent signal to the central nervous system typically occurs, stimulating central processes and autonomic reflexes (3).

Neurogenic Inflammation Hypotheses

General Hypothesis. The structure of the c-fiber system and function of the neuroinflammatory system is altered in people reporting chemical sensitivity.

- People reporting chemical sensitivity have an increased density of c-fiber neurons in tissues where increased sensitivity is reported.
- People reporting chemical sensitivity produce greater quantities of neuropeptides and prostanoids than nonsensitive subjects in response to exposure to low-level capsaicin or irritant chemicals.
- People reporting chemical sensitivity have increased and prolonged responses to exogenously administered c-fiber activators such as capsaicin, as measured by the symptoms, negative mucosal potential, transepithelial potential difference, products of glandular secretion or plasma exudation, or mucociliary clearance.
- People reporting chemical sensitivity demonstrate augmentation of central autonomic reflexes following exposure to agents that produce c-fiber stimulation. For example, trigeminal reflexes are altered in the maxillary and

ophthalmic branches, as evidenced by the CO_2 threshold and/or dose-response function in the nose or eye.

- People reporting chemical sensitivity are less able to inactivate endogenously released neuropeptides because they have decreased quantities of neutral endopeptidase in their epithelium. Agents that alter neutral endopeptidase metabolism alter the symptomatic or objective responses to agent exposure.
- Administering exogenous neuropeptides to PRCS reproduces their symptoms. Activation of the neuropeptide receptor signal transduction process and the transduction process itself is altered in PRCS.
- Residence in an environmental unit alters the threshold or dose-response to c-fiber stimulation in subjects with chemical sensitivity.

Domain 2: Perceptual and Central Integration

Perceptual and central integration is thought to be altered in PRCS for two reasons. First, PRCS commonly complain of alterations in cognitive function. These complaints worsen with exposures but may be present to a lesser extent at baseline. Localization to the central nervous system of exposure-induced symptoms suggests that processes involved with perception or the integration of perception with cognitive functions may be affected. The second reason is that the central nervous system processes are an integral part of the response to a sensory stimulus such as an irritant or an odor (19–24). Anatomic elements of central representation include primary and secondary projection and association areas. Functional elements include quality coding, intensity, cognitive discrimination, hedonic evaluation, and integration of other sensory receptors. Understanding central processes may suggest rational pharmacotherapy (25).

Central and Perceptual Integration Hypotheses

Sensory information processing systems are altered in people reporting chemical sensitivity.

- Patients reporting chemical sensitivity have alterations in adaptation, habituation, cortical representation, perception, cognition and hedonics.
- Adaptation or habituation to repeated chemosensitive stimulation differs between patients with chemical sensitivity and controls.

Habituation refers to the tendency for the amplitude of a response to diminish over time with repeated presentation of the stimulus that elicits the response. The reflexes referred to in the neurogenic inflammation section could habituate or fail to do so in patients reporting chemical sensitivity. In these patients, the reflexes might even become sensitized or show increased reactivity.

Adaptation, in this context, refers to a sensory organ's tendency to show a diminished response as a result of prolonged or repeated stimulation. As a result, perception becomes less salient or appears to be less intense. For example upon entering a room containing an odorant, an individual may perceive an odor to be very strong. Fifteen to thirty minutes later, the odor may be barely noticeable. Chamber studies indicate odor adaptation is strong, reaching perhaps 60% (26,27). Synergy may occur for irritation when exposure to mixtures occurs (28). Sensory irritation, however, shows much less adaptation. People reporting chemical sensitivity may fail to have sensory adaptation or even may have the occurrence of sensitization. Sensitization, in the neurotoxicology field, refers to the development of an augmented response as a result of prolonged or repeated stimulation.

- The qualitative and quantitative interactions between trigeminal and olfactory systems are altered in people reporting chemical sensitivity. Both peripheral and central interactions should be considered.
- Higher integration of sensory inputs is altered in PRCS.

Domain 3: Inflammation

People reporting chemical sensitivity report exposure-induced symptoms persisting for hours to days. Constitutional symptoms such as malaise and fatigue suggest the induction of an inflammatory response. Experimental methods exist to obtain objective evidence for an inflammatory response. Cellular response may include polymorphonuclear leukocytes, lymphocytes, mast cells, eosinophils, and macrophages, whereas the biochemical response can be assessed by measuring serum- or tissue-derived mediators or proteins. There may or may not be evidence for tissue injury at the site of inflammation.

Inflammation Hypotheses

Increased inflammation is present in PRCS, and may be found in the eyes, upper and lower airway, gastrointestinal tract, skin, vascular system, and joints.

- People reporting chemical sensitivity have heightened inflammatory responses

to chemical exposure. This heightened response could be due to physiological and/or anatomical alterations. The temporal relationship between exposures to chemicals and the onset of inflammation reflects the subject's typical exposure-response history.

- Indices of inflammation will resolve with uniform avoidance of stressors, including chemical, physical, emotional, and nutritional stressors, and sleep deprivation.
- The heightened neurosensory response to chemicals in PRCS is associated with the degree of inflammation present at the time of exposure. Pharmaceutical agents that target inflammation will reduce the neurosensory response to irritant chemicals.
- The inflammatory response to chemicals is modified by acute and chronic exposure to chemicals.

Summary and Recommendations

It is reasonable to hypothesize that neurogenic inflammation, perceptual and central integration, and inflammation are involved in the pathogenesis of chemical sensitivity symptoms. Research is recommended to test the hypotheses outlined in this report.

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